



THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Michael J. Heller et al.

Serial No.: 09/912,014

Filed: July 24, 2001

For: Methods for Electronic Synthesis of
Complex Structures

)
) Group Art Unit: 1631

)
) Examiner: Marschel

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SUBMISSION UNDER 37 C.F.R. §1.607 REQUESTING INTERFERENCE

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby submits the information required by 37 C.F.R. §1.607 in order to provoke the requested interference.

Subsection (a):

(1) ***Identification of the Patent(s)*** - Applicant seeks to provoke an interference between the instant application and U.S. Patent Nos. 6,093,302 and 6,280,595 (hereinafter the "'302 patent" and the "'595 patent", respectively, or the "Montgomery patents" collectively), each entitled "Electrochemical Solid Phase Synthesis", each listing Donald D. Montgomery as the sole named inventor.

OC-91789.1

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

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- (2) ***Presentation of Proposed Counts*** - Applicant proposes the following two counts:

Count I

A method for electronic synthesis of an array of separately formed complex structures on a substrate, comprising the steps of:

providing a substrate having an array of controllable electrodes supported by the substrate,

providing first structures coupled to the electrodes, the structures having a blocked functional group,

providing a solution in contact with the array of electrodes,

applying a potential to selected electrodes where synthesis is to occur in order to cause deblocking of the first structure,

reacting a second structure with the deblocked first structure, and

repeating the steps of deblocking and reacting another structure to form the plurality of complex structures.

Count II

A method for electronically controlled synthesis of a plurality of complex structures on a substrate, comprising the steps of:

providing a substrate having a plurality of controllable electrodes supported by the substrate and covered with a permeable layer,

providing first structures coupled to the layer, the structures having a protected functional group,

providing a solution in contact with the array of electrodes
supported by the substrate,

applying a potential to selected electrodes where synthesis is to
occur,

reacting a second structure with the first structure, and

repeating the step of applying a potential and reacting a
subsequent structure to form the complex structures, the synthesis of
the array of structures occurring without mechanical movement.

(3 & 4) *Claims Corresponding to the Proposed Counts:*

Claims corresponding to the Count I:

Heller et al. 95-108, 115, 117-118, 121-136, 139-143, 146-147, 149-156,

Montgomery '302: 15, 17-22, 25-40, 42-44

Montgomery '595: 14-16, 19-37

Claims corresponding to the Count II:

Heller et al. 109, 111-114, 119, 120, 148, 157, 159-170, 174-182, 184-196,

198-199, and 202-204.

Montgomery '302: 23, 24

Montgomery '595: 17, 18

Independent claim 95 corresponds exactly to proposed Count I. Claims 96-108, 115-118, 120-136 and 139-141 correspond substantially to the Count in that they are not identical to the proposed Count I. Dependent claims 109, 111-114 and 119 correspond substantially to proposed Count II.

Independent claim 142 corresponds substantially to Count I in that it is not identical to proposed Count I. As noted in subsection (c), below, independent claim 142 and the dependent claims therefrom find correspondence in the Montgomery '302 patent.

Independent claim 157 corresponds exactly to proposed Count II. Dependent claims 159-171, 173-182, 184-196 and 198-199 correspond substantially to proposed Count II in that they are not identical to the proposed Count.

(5) *Application of the Claims to the Disclosure:*

While the claims corresponding to the Count have been presented previously (in the Preliminary Amendment) and as such, may not require application to the disclosure under 37 C.F.R. §1.607(d)(ii), Applicant nevertheless submits the following correlation chart:

<i>Claim</i>	<i>Specification Support</i>
142. A method for electronic synthesis of an array of separately formed polymers on a substrate, which comprises the steps of:	III(e) <u>COMBINATORIAL BIOPOLYMER SYNTHESIS</u> The devices of this invention are also capable of carrying out combinatorial synthesis of biopolymers such as oligonucleotides and peptides. (p. 53; l. 18-21).
placing a buffering solution in contact with an array of electrodes that is proximate to a substrate surface, said surface being proximate to one or more molecules bearing at least one protected chemical functional group attached thereto,	One method for combinatorial oligonucleotide synthesis is shown in FIGURES 14(A) through 14(F). This method begins with a set of selectively addressable micro-locations (140) whose surfaces have been derivatized with blocked primary amine (X-NH-) groups (142). (p. 54; l. 11-15); As to the microlocations including an electrode proximate the substrate surface, see, e.g., Figs. 1-6 and 14. (See,

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<i>Claim</i>	<i>Specification Support</i>
	e.g., specification p. 25, l. 10-17). As to buffers, see claim 143, below, for specific buffers.
selectively deprotecting at least one protected chemical functional group on at least one of said molecules;	The initial step in the process involves selective deblocking of micro-locations. (p. 54; l. 15-17)
bonding a first monomer having at least one protected chemical functional group to one or more deprotected chemical functional groups of said molecule;	In the second step, chemical coupling of the first base, in this case cytosine, to the deblocked micro-locations is carried out by simply exposing the system to the phosphoramidite reagent (x-C) (146). The cytosine nucleotide couples to deblocked micro-location surfaces, but not to any of the blocked electrode surfaces (FIGURE 14(C) and (D)). (p. 54; l. 27 - p. 55, l. 2)
selectively deprotecting a chemical functional group on the bonded molecule or another of said molecules bearing at least one protected chemical functional group;	At the second de-blocking step (FIGURE 14(D)), those electrode positions which are to be coupled with the next base are made negative. (p. 55; l. 3-6)
bonding a second monomer having at least one protected chemical functional group to a deprotected chemical functional group of the bonded molecule or said other deprotected molecule; and	The system is now exposed to the next base to be coupled, in this case (x-A) (148), and selective coupling to the deblocked micro-location is achieved (FIGURE 14(E) and (F)). (p. 55; l. 6 - 9).
repeating the selective deprotection of a chemical functional group on a bonded protected monomer or a bonded protected molecule and the subsequent bonding of an additional monomer to said deprotected chemical functional group until at least two separate polymers of desired length are formed on the substrate surface.	The coupling and de-blocking procedures are repeated, until all the different DNA sequences have been synthesized on each of the addressable micro-location surfaces. (p. 55; l. 9-12)

<i>Claim</i>	<i>Specification Support</i>
<p>143. A method according to claim 142, wherein said buffering solution is selected from the group consisting of: tris borate buffers, sodium chloride, sodium citrate buffers, and sodium phosphate buffers.</p>	<p>The test devices were pre-run 5 minutes at 0.03 mA in 0.5X TBE (tris borate EDTA) using a Bio-Rad 1000/500 power supply. (p. 81; l. 8-9)</p> <p>Hybridize in 5X SSC (sodium chloride, sodium citrate) for 5 minutes at 20° C</p> <ul style="list-style-type: none"> - "No washing procedure" - Apply an electronic stringency of 0.15 milliamps (mA) at 150 volts (V) (p. 77; l. 5-8) <p>The upper and lower reservoirs are filled with 0.1 M sodium phosphate, pH 7.4 and prerun for 5 minutes at 0.05 mA constant current, using a BioRad 500/1000 power supply. (p. 90; l. 23-26)</p>
<p>146. A method according to claim 142, wherein said monomers are amino acids.</p>	<p>Specific binding entities include, but are not limited to: deoxyribonucleic acids (DNA), ribonucleic acids (RNA), synthetic oligonucleotides, antibodies, proteins, peptides, lectins, modified polysaccharides, cells, synthetic composite macromolecules, functionalized nanostructures, synthetic polymers, modified/blocked nucleotides/nucleosides, modified/blocked amino acids (p. 13; l. 15-21)</p> <p>See also original claim 70 ("said monomer-A consists of an amino acid...")</p>
<p>147. A method according to claim 142, wherein said molecules are linker molecules or monomers.</p>	<p>This method begins with a set of selectively addressable micro-locations (140) whose surfaces have been derivatized with blocked primary amine (X-NH-) groups (142). (p. 54; l. 11-15)</p>
<p>148. A method according to claim 142, wherein said molecules are attached to a layer of material overlaying said substrate surface.</p>	<p>The surface of each micro-location has a permeation layer for the free transport of small counter-ions, and an attachment layer for the covalent coupling of specific binding</p>

<i>Claim</i>	<i>Specification Support</i>
	entities. (p. 13; l. 33 - p. 14; l. 5)
149. A method according to claim 142, wherein said substrate is formed from at least one material selected from silicon, glass, ceramics, silicon dioxide and plastic.	Fabrication is carried out on silicon or other suitable substrate materials, such as glass, silicon dioxide, plastic, or ceramic materials (p. 24; l. 17-19)
150. A method according to claim 142, wherein said array of electrodes comprises at least 64 electrodes.	See Fig. 3 which includes 64 microlocations and Fig. 5 which includes 96 microlocations. The number of locations can range from several to at least hundreds of thousands. (p. 14; l. 20-21).
151. A method according to claim 150, wherein said array of electrodes comprises a matrix having hundreds of thousands of electrodes.	The number of locations can range from several to at least hundreds of thousands. (p. 14; l. 20-21)
152. A method according to claim 142, wherein each of the electrodes in said array ranges in diameter from less than 0.5 micron to about 200 microns.	Addressable micro-locations can be of any shape, preferably round, square, or rectangular. The size of an addressable micro-location can be of any size, preferably range from sub-micron ($\sim 0.5 \mu\text{m}$) to several centimeters (cm), with $5 \mu\text{m}$ to $100 \mu\text{m}$ being the most preferred size range. (p. 23, l. 24-29) See also original claim 26 ("wherein the width of the binding locations on the device is between 0.5 microns and 200 microns.")
153. A method according to claim 142, wherein the electrodes of said array are formed from platinum or palladium.	The electronic device of claim 1, wherein said electrode comprises a material selected from a group consisting of ... platinum, palladium (p. 30; l. 21)
154. A method according to claim 142, which further comprises an additional bonding step wherein a pre-formed molecule is bonded to a deprotected chemical functional group on one or more of said molecules or monomers.	Specific binding entities include, but are not limited to: deoxyribonucleic acids (DNA), ribonucleic acids (RNA), synthetic oligonucleotides, antibodies, proteins, peptides, lectins, modified polysaccharides, cells, synthetic composite macromolecules, functionalized nanostructures, synthetic polymers, modified/blocked

<i>Claim</i>	<i>Specification Support</i>
	nucleotides/nucleosides, modified/blocked amino acids... (p. 13; l. 15-21) See also original claim 70
155. The method according to claim 142 wherein the monomer is a nucleotide.	In the second step, chemical coupling of the first base, in this case cytosine, to the deblocked micro-locations is carried out by simply exposing the system to the phosphoramidite reagent (x-C) (146). The cytosine nucleotide couples to de-blocked micro-location surfaces, but not to any of the blocked electrode surfaces (FIGURE 14(C) and (D)). (p. 54; l. 27 - p. 55; l. 1)
156. A method according to claim 142 wherein a structure which scavenges adverse materials produced in an electrolysis reaction is situated proximate to one or more of said electrodes.	<p>"The permeation layer can also be designed to include substances which scavenge adverse materials produced in the electrolysis reactions (H₂, O₂, free radicals, etc.)". (p. 32; l. 27-29)</p> <p>These micro-locations or macro-locations can be used to store reagents, to temporarily hold reactants, analytes, or cells, and as disposal units for excess reactants, analytes, or other interfering components in samples. (p. 28; l. 10-14)</p>

The following table further identifies support for other claims added by the Preliminary Amendment. The representative support references the claim number utilized in the chart, above, and further references the specification.

<i>Claim No.</i>	<i>Representative Support</i>
95	142
96-106, 159-169	142, 146
107, 170	150
108	Spec p. 53, l. 21-23
109-114, 174-177	See 148 and also Spec p. 33, l. 1 - p. 35, l. 4
115, 117, 118, 178-181	156
119, 182	148

<i>Claim No.</i>	<i>Representative Support</i>
121, 122, 184, 185	142
123, 186	142 and also Spec p. 53, l. 32
124, 125, 187, 188	142 and also Spec p. 54, l. 17
126-128, 189-191	152
129, 130, 192, 193	142 and also Spec p. 54, l. 3-6
131-135, 194-197	142 and also Spec p. 54, l. 1
136, 139, 140, 202, 203	143
141-204	142
157	142, 148

(6) *Compliance with 35 U.S.C. §135(b):*

All claims were presented within one year after the issue date of the Montgomery '302 and '595 patents.

Subsection (c):

Heller et al. application claims 142, 143, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, and 156 correlate to Montgomery '302 claims 15, 18, 21, 22, 23, 27, 28, 30, 31, 32, 35, 40, and 43, respectively.

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Conclusion

Applicant requests that the prosecution for the instant application be conducted with special dispatch as required by 37 C.F.R. §1.607(b), and that the requested interference be declared.

Respectfully submitted,

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Dated: September 21, 2001

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